

Notice of Allowability

Application No.

10/699,393

Examiner

Sheridan L. Swope

Applicant(s)

GRUBER ET AL.

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to January 18, 2007.
2. ☒ The allowed claim(s) is/are 1,2,6,7,16-18,44 and 45.
3. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some* c) ☐ None of the:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.

THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

4. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
- (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
- 1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
- (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.
- Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).
6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

- | | |
|--|---|
| 1. <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 5. <input type="checkbox"/> Notice of Informal Patent Application |
| 2. <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 6. <input type="checkbox"/> Interview Summary (PTO-413),
Paper No./Mail Date _____ |
| 3. <input type="checkbox"/> Information Disclosure Statements (PTO/SB/08),
Paper No./Mail Date _____ | 7. <input checked="" type="checkbox"/> Examiner's Amendment/Comment |
| 4. <input type="checkbox"/> Examiner's Comment Regarding Requirement for Deposit
of Biological Material | 8. <input checked="" type="checkbox"/> Examiner's Statement of Reasons for Allowance |
| | 9. <input type="checkbox"/> Other _____ |

DETAILED ACTION

Applicant's response, on January 18, 2007, to the Final Rejection of August 24, 2006 and the Advisory Action of November 17, 2006, is acknowledged. It is acknowledged that Applicants have cancelled Claim 5 and amended Claims 1, 2, 6, 7, 16-18, 44, and 45. Claims 1-4 and 6-58 are pending. Claims 3, 4, 8-15, 19-43, and 46-58 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions. Claims 1, 2, 6, 7, 16-18, 44 and 45 are hereby reconsidered.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of Claims 1, 2, 5-7, 16, and 18 under 35 U.S.C. 112, first paragraph, is withdrawn for the following reasons. The means by which the function of thrombin is regulated by its structure has been well characterized (Tsiang et al, 1995; Richardson et al, 2000). Therefore, it would not be undue experimentation for the skilled artisan to make and use the full scope of the recited thrombin variants; Applicants were in possession of their recited invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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The prior rejection of Claims 1, 2, 6, 7, 16-18, 44, and 45 under 35 USC 103(a) over Gibbs et al, 1996 in view of Arosio et al, 2000 or Ayala et al, 2001 is withdrawn for the following reasons. Said prior rejection was based on the fact that both the W²¹⁵A (Arosio et al or Ayala et al) and E²¹⁷A (Gibbs et al) substitutions were known in the art and that skilled artisan would be motivated to make a W²¹⁵A + E²¹⁷A thrombin variant because there was an expectation that said variant would have a higher PA/FC compared to either W²¹⁵A thrombin or E²¹⁷A thrombin. However, the extent of synergy resulting from the double W²¹⁵A + E²¹⁷A mutation is far greater than expected. As disclosed by Applicants' analysis in Exhibit A, filed January 18, 2007, the single mutation E²¹⁷A gives a PA/FC of 19.1 (Gibbs et al; Table 1), the single mutation W²¹⁵A gives a PA/FC of 170 (Arosio et al; Table 1), while Applicants' W²¹⁵A + E²¹⁷A thrombin variant has a PA/FC of 2865. Such dramatic synergy is far greater than expected and, as such, the unexpected results overcome the prior obviousness rejection (MPEP 716.02(c)). For these reasons, rejection of Claims 1, 2, 6, 7, 16-18, 44, and 45 under 35 USC 103(a) over Gibbs et al, 1996 in view of Arosio et al, 2000 or Ayala et al, 2001, is withdrawn.

Examiner's note: Applicants define the term "PA/FC ratio" as the ratio of the percent of wild-type protein C activation (PA) activity remaining in a thrombin variant relative to the percent of wild-type fibrinogen clotting (FC) activity remaining in the thrombin variant. A value of PA/FC greater than 1.0 indicates that the thrombin variant has reduced procoagulant fibrinogen cleavage activity relative to the residual anticoagulant activity resulting from protein C activation.

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Examiner's Amendment

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to Applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Claims

Cancel Claims 3, 4, 8-15, 19-43, and 46-58.

Replace Claims 1, 17, 18, and 44 with:

1. A protein comprising a variant thrombin, wherein the variant thrombin is at least 80% identical to the sequence set forth by SEQ ID NO: 3 and comprises the residues corresponding to Ala²⁶³ and Ala²⁶⁵ of SEQ ID NO: 3, and wherein the variant thrombin has a PA/FC ratio greater than 1.0.

17. The physiologically acceptable composition according to claim 16, wherein the variant thrombin has the amino acid sequence set forth by SEQ ID NO: 3.

18. The physiologically acceptable composition according to claim 16, wherein the variant thrombin has the amino acid sequence set forth by SEQ ID NO: 4.

44. A kit comprising the variant protein of claim 1 or 2 and packaging comprising instructions for using the protein as an antithrombotic agent in a recipient animal or human.

Authorization for this examiner's amendment was given in a telephone interview with Tim Xia on January 30, 2007.

Allowable Subject Matter

Claims 1, 2, 6, 7, 16-18, 44 and 45 are allowed.

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The following is an examiner's statement of reasons for allowance:

All allowed claims, Claims 1, 2, 6, 7, 16-18, 44 and 45, are limited to a protein comprising a thrombin variant, wherein the thrombin variant has a PA/FC ratio of greater than 1.0, has at least 80% identity to SEQ ID NO: 3 or 4, and has substitutions corresponding to W²¹⁵A and E²¹⁷A of wild-type thrombin according to the Sadler numbering system (Wu et al, 1991; IDS), wherein said substitutions correspond to Ala²⁶³ and Ala²⁶⁵ of SEQ ID NO: 3 and Ala²²⁷ and Ala²²⁹ of SEQ ID NO: 4. The utility of the thrombin variants set forth by SEQ ID NO: 3 and 4, as having a PA/FC ratio of greater than 1.0, is credible based on recombinant expression and analysis of protein C activation and fibrinogen clotting (Table 2). Furthermore, as described above, the dramatically unexpected increase in the PA/FC ratio upon mutation of both W²¹⁵A and E²¹⁷A renders the thrombin variants of SEQ ID NO: 3 and 4 non-obvious to the skilled artisan. Said thrombin variants have real-world use as anti-coagulants. Therefore, the recited invention has a specific and substantial, patentable utility.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

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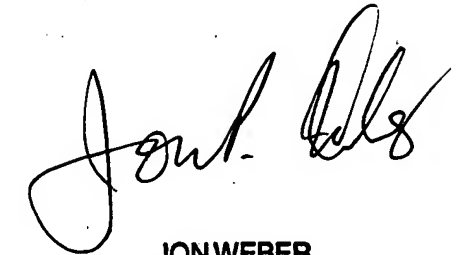
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
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SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER



JON WEBER
SUPERVISORY PATENT EXAMINER